Acute respiratory distress syndrome (ARDS) is a condition characterized by a high permeability oedema due to loss of the integrity of the alveolo-capillary barrier with impairment of normal surfactant function, resulting in an increased collapse tendency of the alveoli. Mechanical ventilation on such alveoli with repeated alveolar collapse and subsequent reexpansion results in severe lung parenchymal injury and may induce further surfactant impairment. This can be prevented by maintaining alveolar volume at end-expiration by means of sufficient levels of positive end-expiratory pressure (PEEP). Recent evidence from experimental studies has shown that ventilator modes which allow end-expiratory collapse can induce bacterial translocation from the lung into the bloodstream and trigger the release of inflammatory mediators, which can also be presented by maintaining end-expiratory alveolar volume. These data suggest that the interaction between surfactant changes and mechanical ventilation may play a role in the transition of ARDS into the systematic inflammatory disease process of multiple system organ failure (MSOF).

**Key words:** acute respiratory distress syndrome, alveolo-capillary barrier, positive end-expiratory pressure, bacterial translocation, multiple organ failure.

**INTRODUCTION**

Acute respiratory distress syndrome (ARDS) has become a well-recognized condition that can result from a number of different causes, e.g. sepsis, shock, pneumonia, trauma, liquid aspiration, haematologic disorders, smoke inhalation and many others (1). Despite diverse etiologies of ARDS, the final common pathway results in damage of the alveolar epithelium and endothelium, which leads to high permeability oedema. The exact mechanisms responsible for injury to the alveolo-capillary membrane are complex and still under discussion (2).

Plasma components in the pulmonary edema, such as fibrin (ogen), are able to inactivate surfactant in a dose-dependent way (3). Diminished surfactant
function in ARDS leads to an increase in forces acting at the air-liquid interface of the alveolus, finally resulting in end-expiratory alveolar collapse, atelectasis, an increase in right-to-left shunt and a decrease in PaO₂. Such changes necessitate the use of high inspiratory oxygen concentrations and mechanical ventilation to maintain adequate oxygen delivery to the tissues. This sequence of events in ARDS is schematically depicted in Fig. 1.

Fig. 1. Schematic presentation of the sequence of events that necessitates the use of mechanical ventilation in acute respiratory distress syndrome (ARDS).

Despite such ventilatory supportive measures, the mortality rate of ARDS has not significantly decreased since it was first described in 1967 (4); mortality rates are reported to range from 10 to as high as 90%, with an average of 50% (5). Approximately 50% of patients with an unresolved ARDS will develop MSOF (6, 7) which has become the leading cause of death in ARDS (6). ARDS usually predates other organ failures and the majority of patients with MSOF develop ARDS as the initial organ failure (7). Therefore, ARDS is not solely regarded as a primary pulmonary disease process but rather as an important and possibly causative part of an inflammation-induced systematic disease state that can evolve to MSOF (8).

Recent studies show that the mode of ventilation may be an important factor influencing mortality from ARDS (5, 9). Mechanical ventilation can induce lung parenchymal damage especially in the surfactant deficient parts of the ARDS lung and may further induce surfactant changes in those parts of the ARDS lung which still have an adequately functioning surfactant system (10). Moreover, mechanical ventilation may play an important role in inducing local inflammatory reactions in the lung and, via a systemic spread of inflammatory mediators and bacteria, the inflammatory disease process of MSOF.
This paper will focus on the role of surfacant changes in lung injury and recent investigations in the field of ventilator-induced lung injury. An optimized ventilation strategy to avoid ventilator-induced lung injury is presented.

**SURFACTANT CHANGES IN ARDS**

Ashbaugh et al. were the first to demonstrate decreased lung compliance and increased minimal surface tension in lung extracts from patients with ARDS (4). Since then, several studies have demonstrated qualitative and quantitative changes of surfactant in bronchoalveolar lavage (BAL) fluid from patients with ARDS (for review see 11, 12). Alteration in the phospholipid profile consists of decreased levels of phosphatidylcholine and phosphatidylglycerol, and increased levels of aphiingomyelin and lyso-phosphatidylcholine.

Surfactant changes in ARDS are not restricted to compositional changes. The pulmonary surfactant system can be divided into two distinct subfractions by centrifugation: denser or large surfactant aggregates, and lighter or small surfactant aggregates (13). The large aggregates are the metabolic precursors of the small aggregates and are the surface-tension reducing components (14) guaranteeing end-expiratory alveolar stability, whereas the small aggregates possess poor surface activity both in vitro (15) and in vitro (16). Studies by Veldhuizen showed that there is an important increase in the ratio of small aggregates to large aggregates in the BAL fluid recovered from patients with ARDS (17).

Gregory et al. (18) showed that minimal surface tension was increase and total phospholipids and surfactant proteins were decreased in the BAL fluid obtained from 66 ARDS patients. In addition, this group observed that several of these alterations also occur in patients at risk of developing ARDS, suggesting that these surfactant abnormalities occur early in the disease process (18).

**CONSEQUENCES OF MECHANICAL VENTILATION ON THE SURFACTANT-DEFICIENT LUNG**

More than 20 years ago, Mead et al. stated that: “at a transpulmonary pressure of 30 cm H₂O, the pressure tending to expand an atelectatic region surrounded by a fully expanded lung would be approximately 140 cm H₂O” (19). During ventilation of patients with ARDS, who almost always have atelectatic lung regions due to surfactant deficiency, transpulmonary pressure differences of 30 cm H₂O or higher are quite common. We have to understand, however, that it is not the 30 cm H₂O transpulmonary pressure difference that damages the lungs but rather the resulting shear forces of more than 140 cm H₂O, that develop due to pulmonary interdependence of alveoli, which are responsible for the barotrauma. Such forces may be the major cause of
structural damage (especially to bronchiolar epithelium, alveolar epithelium and capillary endothelium) in ARDS (20).

Recent findings in isolated, nonperfused lavaged surfactant-depleted rat lungs ventilated with normal tidal volumes at different end-expiratory pressures, have shown that lungs ventilated below the infection point of their P-V curve, representing the point of alveolar closure, showed significantly more morphological lung injury than lungs ventilated above this point (21). A recent study in a model of subtle surfactant perturbation by dioctyl sodium sulfoseekinate, which does not lead to any other damage of the alveolo-capillary barrier, showed that surfactant changes make the lung vulnerable to lung parenchymal injury by mechanical ventilation (22). These results point towards an important interaction of mechanical ventilation and surfactant impairment in inducing lung epithelial changes. These data confirm earlier work of Nilsson in ventilated premature newborn rabbits with a primary surfactant deficiency. Fetuses treated with surfactant before mechanical ventilation had less bronchiolar epithelial lesions in comparison to non-surfactant treated controls (23).

It is now becoming increasingly realized that mechanical ventilation itself can induce severe perturbation of the surfactant system.

SURFACTANT CHANGES INDUCED BY MECHANICAL VENTILATION

Pioneering work of Mead in 1959 showed that mechanically ventilated dogs had a progressive fall in pulmonary compliance, which could be reversed by periodic forced inflations of the lung (24). Greenfield and coworkers related such ventilator-induced mechanical changes to the pulmonary surfactant system by demonstrating increased surface tensions of lung extracts in dogs ventilated with peak inspiratory pressures of 28—32 cm H$_2$O for 1 to 2 hours (25). These findings were later confirmed by others (26—28).

Research has shown that four mechanisms are involved in the alteration of surfactant function during mechanical ventilation: 1) loss of surfactant into the smaller airways 2) conversion of surface active large into less-surface active small aggregates. This will result in increased surface tension conditioned suctioning over the alveolo-capillary barrier and 3) inactivation of surfactant due to ventilation-induced protein-rich edema. Lastly, 4) loss of surfactant components into the bloodstream has been described.

Loss of surfactant into the smaller airways

It is known that mechanical ventilation enhances the release of surfactant from pneumocytes type II into the alveolus (25—28). This released material may be lost from the alveoli as a result of compression of the surfactant film
when the surface of the alveolus becomes smaller than the surface occupied by the surfactant molecules and subsequent movement of surface-active material into the airways (29, 30) (Fig. 2). The mechanism of surfactant depletion due to

**Fig. 2.** (A) Balance between synthesis, release and consumption of surfactant in the healthy lung. The pressure values given represent the intrapulmonary pressure needed to open up the alveolus. At the surface and the hypophase (micelles), there are sufficient molecules of surfactant. These micelles deliver the surfactant necessary to replace the molecules squeezed out during expiration.

(B) Imbalance between synthesis, release and consumption of surfactant due to artificial ventilation. At the beginning of inspiration, there exists an apparent deficiency of surfactant molecules but there is a respreading of molecules stored in the hypophase of the surfactant layer. At the end of inspiration there is, in principle, enough surfactant on the surface.

(C) With the next expiration, surface active molecules are squeezed out and no surface active molecules are left in the hypophase for respreading, creating the situation where a serious surfactant deficiency follows.
mechanical ventilation was proven by Faridy et al. who showed that mechanical ventilation increases the surface activity of lavage fluid recovered from the pulmonary airways (30). This change in surface activity increased with the duration of ventilation and the tidal volume used (30). Studies by Wyszogrodski et al. have shown that positive end-expiratory pressure (PEEP) prevents a decrease in lung compliance and surface activity of lung extracts, indicating preservation of the alveolar surfactant loss (29). It was suggested that PEEP prevents alveolar collapse and thus loss of surfactant into the small airways during expiration (31) (Fig. 2).

Conversion of surface active large aggregates into less-surface active small aggregates

The surfactant system can be divided by differential centrifugation into surface tension lowering large tubular myelin like forms of surfactant and less-surface tension lowering small surfactant aggregates, which represent small vesicular structures. To maintain an adequate pool of surface tension lowering large surfactant aggregates in the airspaces, it is necessary to maintain a balance between secretion, uptake and clearance of large and small aggregates (14). In vivo experiments in rabbits showed that tidal volume is the main determinant for the conversion of large into small surfactant aggregates (32, 33) (Fig. 3A vs B). The same studies demonstrated that changing the respiratory rate (32) or the level of PEEP (33) did not affect the rate of aggregate conversion.

Inactivation of surfactant due to ventilation-induced protein-rich edema

The pulmonary surfactant system has an important function in stabilization of the fluid balance in the lung and protection against lung oedema (34, 35). Together with the interstitial colloid osmotic pressure and the capillary hydrostatic pressure, the surface tension at the air-liquid interface opposes the plasma colloid oncotic pressure (36). Mechanical ventilation with high peak inspiratory lung volumes leads to structural damage of the alveolo-capillary barrier and this to intra-alveolar oedema (37). (Fig. 3B). The accumulation of protein rich oedema fluid dilutes (38) and inactivates the pulmonary surfactant system (2, 39—41). An increase of the surface tension at the air-liquid interface of the alveoli, with more surface tension conditioned suctioning over the alveolo-capillary barrier and development of intra-alveolar oedema is the result.

Eventually, this will lead to a self-triggering mechanism of surfactant inactivation. PEEP has been shown to reduce the amount of oedema and present intra-alveolar oedema formation (42, 43).
Loss of surfactant into the bloodstream

Due to damage of the alveolo-capillary barrier, surfactant components may translocate into the bloodstream. Surfactant protein A has been shown to translocate from the alveolar spaces into the bloodstream due to injury of the alveolo-capillary barrier as a result of mechanical ventilation and to be an indicator of alveolo-capillary membrane injury in ARDS (44, 45) (Fig. 3B). Moreover, damaging the alveolo-capillary barrier by means of intravenous injection of an anti-lung serum (46) in rabbits, resulted in loss of radioactively labelled phospholipids from the lungs of which 82% was recovered in the liver (46).

These mechanisms of functional surfactant impairment due to mechanical ventilation have been schematically depicted in Fig. 3A and B. We will now focus on the role of the interaction between (ventilator-induced) surfactant changes with tissue disruption in the transition of ARDS into MSOF.

BACTERIAL TRANSLOCATION AND ENDOTOXIN RELEASE INTO THE BLOOD STREAM IN MSOF

Bacterial translocation from the gut

Damage to the intestinal mucosa with a resulting alteration in gut barrier function to bacteria and subsequent increased bacterial translocation to the bloodstream has been shown to be a major cause of bacteremia after severe shock and trauma (47, 48) and was recognized as early as 1966 (49). Clinical results with selective decontamination of the digestive tract by means of non-absorbable antibiotics to reduce nosocomial infections and length of stay in the intensive-care unit remain controversial. There is general consensus about the efficacy of decontamination in diminishing microbial carriage and acquired infection rates, although conclusions about benefits related to mortality vary (50—53).

Bacterial translocation from the lung

Patients on ventilatory support often develop a ventilator-associated pneumonia (VAP) with predominantly aerobic Gram-negative bacilli. Reported incidence rates for VAP in ventilated patients range from 9 to 70%, to as high as 92% in a particular subset of ultimately fatal patients (54). Most authors agree that gastric colonisation by Gram-negative bacilli with subsequent aspiration of gastric contents is the main determinant of the development of VAP with Gram negative bacilli (55), but other risk factors, such as duration of mechanical ventilation, use od PEEP, hospitalization
Type II cell

ER/Golgi stores

Large Aggregates
Small Aggregates
Protein inactivated surfactant
Bacteria

Capillary
Protein

Surfactant
Shear Stress

Type II cell
ER/Golgi depletion

LA↓

Surfactant
Opsonization↓

Protein↓
Sp-A
Phospholipids
Fig. 3. Simplified diagrams showing. (A) Homeostasis in the normal alveolus: there is a balance between secretion uptake and clearance of large surfactant aggregates and small surfactant aggregates with sufficient endoplasmatic reticulum and Golgi complex stores of surfactant; there is a proper barrier function of the alveolar endothelium and endothelium and plasma proteins are confined to the capillary lumen; there are sufficient surfactant molecules to form a monolayer covering the whole alveolar surface; all alveoli are open at end-expiration; there is an adequate macrophage function with proper bacterial opsonisation.

B) Disturbance of homeostasis by mechanical ventilation with high peak inspiratory lung volumes without PEEP: There is an increased conversion of large surface tension lowering aggregates into non-surface tension lowering small aggregates; endoplasmatic reticular and Golgi complex surfactant stores are depleted; surfactant is lost at end-expiration into the small airways; the barrier function of the alveolo-capillary barrier to protein is lost first at the capillary and later at the epithelial level resulting in intra-alveolar protein influx and surfactant inactivation; there are insufficient surfactant molecules to form a properly functioning surfactant monolayer; alveoli start to collapse at end-expiration resulting in shear forces on the alveolar epithelium; proper bacterial opsonization may become impaired; a ventilator associated pneumonia may develop (with predominantly Gram negative bacteria).

(C) Alveolar epithelium is disrupted and a Gram negative bacteremia develops together with an endotoxemia; inflammatory mediators are released from the endothelium, epithelium and macrophages due to stimulation of stretch receptors and are released into the bloodstream.

Abbreviations: SA: small aggregates; LA: large aggregates; ER: Endoplasmatic reticulum; Golgi: Golgi complexes; MØ: macrophage; Sp-A: surfactant protein-A.
period prior to mechanical ventilation, prior antibiotic administration, chronic obstructive pulmonary disease, reintubation, age and thoracic/upper abdominal surgery, have been identified too (56).

Nowadays, both human and animal studies have shown that pneumonia results in significant changes in pulmonary surfactant composition and function e.g. increased surface tensions, decreased amounts of phospholipids, a shift in the phospholipid or fatty acid profile and changes in surfactant proteins of lung extracts and lavage samples (57). As explained, in lungs with surfactant changes, mechanical ventilation poses an extra risk factor for injury to the alveolo-capillary barrier.

As early as 1888, Büchner suggested the direct passage of bacteria from infected alveoli into the bloodstream (58). Tuttle and Cannon found evidence that intratracheal injected hemolytic streptococci in rabbits, passed directly from the lung through the vessel wall into the bloodstream (59). This was deduced from the rapid appearance of positive blood cultures and the only rare recovery of bacteria from the lymphatics (59), which suggested that the bacteria bypassed the lymphatic system. However, such findings were not confirmed for pneumococci, which invariably passed the lymphatics before reaching the bloodstream (60). At present, little is known about the interaction between surfactant and lung epithelial changes induced by mechanical ventilation and bacterial translocation from the lung into the bloodstream in VAP.

The high inspiratory oxygen concentrations used during mechanical ventilation in ARDS patients, which induce lung injury due to generation of toxic oxygen radicals, may play an important role in inducing translocation of bacteria from the lung to the bloodstream. Studies by Johanson and coworkers showed that hamsters infected with $5 \times 10^6$ CFU of Pseudomonas aeruginosa and breathing air had no bacteremia after 7 days, whereas some animals breathing oxygen had bacteremia related to oxygen-induced pulmonary lesions (61).

Studies on the effect of different ventilator settings and the interaction with surfactant changes are scarse. Tilson et al. conducted experiments to test whether 10 cm H$_2$O PEEP has a beneficial effect on the course of infection during 24 h of volume-controlled mechanical ventilation 50% oxygen — 50% N$_2$O at a tidal volume of 16 cc/kg and a respiratory rate of 10 bpm) in dogs inoculated endotracheally with $1 \times 10^9$ Pseudomonas aeruginosa organisms/kg compared to dogs ventilated without PEEP at the same ventilator settings (62). Non-infected control dogs ventilated with or without PEEP survived the end of the 24 hour study period as did all of the infected animals ventilated with 10 cm H$_2$O PEEP. Three out of 4 infected animals ventilated without PEEP died before the end of the study period at 10, 15 and 21 hours. PEEP had a positive effect on the course of the infection and the bacterial count recovered from the lung parenchyma were lower in the animals treated with PEEP (62). Interestingly, two out of four infected animals ventilated without PEEP had
positive terminal blood cultures for Pseudomonas, whereas none of the PEEP treated animals developed positive blood culture (62).

In a recent preliminary report by Nahum et al. 3 groups of dogs were inoculated with $10^8$ CFUs E. Coli by intratracheal instillation (63). One group was ventilated with a low PEEP (3 cm H$_2$O) and low tidal volume (resulting in peak transpulmonary pressures of $\leq 15$ cm H$_2$O), a second group was ventilated with a low PEEP and high tidal volume (generating peak transpulmonary pressures of 35 cm H$_2$O) and a third group with high PEEP (10 cm H$_2$O) in which the tidal volume was adjusted to give a peak pressure of 35 cm H$_2$O. It was shown that avoiding high peak transpulmonary pressures or preserving end-expiratory lung volume with PEEP prevents bacterial translocation from the alveoli into the bloodstream (63).

These data strongly suggest that ventilation-induced changes in the barrier function of the lung endothelium and epithelium contribute to the development of bacteremia and endotoxemia as it is seen in MSOF (Fig. 3C). The use of high peak inspiratory pressures together with high inspiratory oxygen concentrations appear to induce translocation of bacteria from the lung into the bloodstream, whereas the use of PEEP appears to be a protective factor for depletion of surfactant and thus for ventilation-induced bacterial translocation.

**VENTILATION-INDUCED MEDIATOR RELEASE**

Although bacteremia and endotoxemia play an important role in the induction and maintenance of MSOF, a focus of infection is not required for an ARDS and MSOF to develop (8). It now appears that the immune inflammatory system play a major role in the pathophysiology of MSOF, and that the host's own endogenous mediators may contribute to organ failure (64, 65).

A vast number of proinflammatory systems and substances have been identified to play a role in ARDS and MSOF. Very soon after the initial description of ARDS in 1967, alterations in the blood clotting system and the activation of the complement cascade were considered as causative factors in the pathogenesis of ARDS. Later, the release of inflammatory mediators from the lung was described. Thesw include: 1) ischaemia-reperfusion events with conversion of xanthine oxidase to xanthine dehydrogenase leading to the release of oxygen radicals; 2) oxygen radicals and proteases released by polymorphonuclear cells; 3) local release of prostanoids and leukotrienes from the arachidonic acid cascade; 4) platelet activating factor release after phospholipase A$_2$ activation; 5) cytokine release; release of vascoactive amines (histamine, serotonin, kinins and catecholamines); 6) release of nitric oxide from nitric oxide synthases (NOS); and 7) circulating immune complexes. Additionally, hormonal changes and neural influences from the central nervous
system were shown to aggravate the acute lung injury; the role of proimflammatory systems and substances in MSOF has been described elsewhere (8, 64—67).

Important sites of inflammatory mediator release from the lung are: neutrophils that have adhered to the lung endothelium; alveolar macrophages; blood platelets and the capillary endothelium (8). Over the past decade information has emerged which indicates that the alveolar epithelium is likely to be involved in a broad range of inflammatory processes within the lung (68). However, the concept of ventilator-induced mediator expression as a result of either damage to the endothelial or epithelial cells or stimulus of stretch receptors present on endothelial cells (69), macrophages (70) and epithelial cells (71) is new (Fig. 3C).

Evidence for the release of cytokines during ventilation is limited. A study by Imai et al. investigated the appearance of the inflammatory chemical mediators platelet-activating factor (PAF), Tromboxane (TX) B2 and 6-keto-prostaglandin (PG) F1α in BAL fluid in surfactant-depleted rabbit lungs during conventional and high frequency oscillatory ventilation (72). One group of animals was ventilated with conventional mechanical ventilation with a peak inspiratory pressure of 25 cm H2O, a PEEP of 5 cm H2O and a mean airway pressure of 15 cm H2O at an FiO2 of 1.0 and a respiratory rate that was adjusted to maintain PaCO2 between 30 and 50 mmHg. Two other groups of rabbits were ventilated with high frequency oscillation at a frequency of 15 Hz, a mean airway pressure of 15 cm H2O, a normocapnia that was maintained by altering the stroke volume of the piston and with FiO2s of 0.21 and 1.0, respectively. Conventional mechanical ventilation resulted in higher mediator levels in the lavage fluid than high frequency oscillatory ventilation. There were no differences in the HFOV animals exposed to either 21% or 100% oxygen. These data show that HFO which produces less shear forces in the lung compared to CMV, prevents the release of inflammatory chemical mediators (72).

Such findings have recently also been demonstrated for the intra-alveolar expression of m-RNA of TNF-alpha which was increased after 1 hour of CMV, whereas high frequency ventilation produced less increase in m-RNA for TNF-alpha (73). These data were confined to measurements on the BAL fluid. However, a recent preliminary report by von Bethmann et al. shows that there is also release of the mediators prostracyclin, tumor necrosis factor α and interleukin-6 after artificial ventilation into the lung perfusate of isolated perfused and ventilated mouse lungs (74). It was observed that the mRNA for TNF was upregulated after 30 min of hyperventilation, while production of TNF increased during the following 120 minutes of hyperventilation. IL-6 was released later than TNF and the IL-6 mRNA was not elevated at 30 minutes (74). In a subsequent study, the effect of 30 minutes of hyperventilation followed by 120 minutes of normal of continuous hyperventilation. It was
shown that a continuous stimulation by hyperventilation is necessary for TNF release whereas a short period of 30 minutes of hyperinflation is sufficient to stimulate release of IL-6 for the next 120 minutes (75). Recently, Berg et al. reported that hyperventilation induced the mRNA of another cytokine, i.e. TGF-β (76).

Studies by Tremblay and coworkers investigated the effect of different ventilation strategies on lung inflammatory mediator expression and production, e.g. TNF α, IL-1β, IL-6, IL-10, MIP-2 and IFN-γ in the presence and absence of a preexisting inflammatory stimulus (77). Rats were given either saline (control) or lipopolysaccharide (LPS) i.v. and after 50 minutes of spontaneous respiration, the lungs were excised and randomized to 2 h of ventilation with different strategies. It was shown that mechanical ventilation with high peak inspiratory lung volumes and 0 cm H₂O PEEP have a synergistic effect on cytokine levels in the lung. Ten cm H₂O of PEEP at comparable peak inspiratory lung volumes or lowering peak inspiratory lung volume when ventilating with zero PEEP reduced these cytokine levels. This occurred in lungs with and without preexisting inflammatory stimuli (77).

When such experimental findings apply to the clinical situation, even moderate artificial mechanical ventilation may elicit pulmonary inflammation. This would have serious consequences for the practice of mechanical ventilation. Inactivation of released cytokines could help contain the inflammatory response induced by mechanical ventilation by scavenging such proinflammatory substances. Recent animal investigations suggest that treatment with anti-bodies directed against specific mediators may reduce pulmonary injury. In rabbits subjects to pulmonary lavage and 8 hours of hyperoxia and hyperventilation, treatment with an IL-1 receptor antagonist reduced lung injury as evidenced by significantly lower concentration of albumin and elastase and lower neutrophil counts in their lungs after ventilation period (78).

Given the huge range of inflammatory mediators involved in the process of ARDS and MSOF, the best containment of the inflammatory response in the lung is probably achieved by prevention of the principal cause of such inflammatory mediators, which is reduction of mechanical stretch of the lung parenchyma. This may have consequences for the systemic inflammatory disease state and mortality from ARDS and MSOF. There are important indicators that a lung protective strategy reduces mortality in ARDS patients (79, 80).

**LUNG SPECIFIC THERAPEUTIC INTERVENTIONS IN ARDS THAT REDUCE MORTALITY**

New immunological treatment approaches in ARDS directed against specific parts of the inflammatory cascade, do not result in a significant
reduction in mortality (66, 81—88). Due to the complexity and redundancy of the inflammatory network it is likely necessary to combine these new agents to improve survival in clinical trials (66). Recently, however, two preliminary reports showed a reduction in mortality in ARDS by the use of exogenous surfactant therapy in one study (79) and by mechanical ventilation with maintenance of end-expiratory pressures above the lower inflection point of the pressure-volume-curve of the lung in combination with low tidal volumes and pressure limited models of ventilation in the other (80).

The first study, a multicenter, randomized pilot study, was performed by Gregory et al. in 59 patients with ARDS of different etiologies (79). In this study, four different dosing strategies were tested, and the results showed that maximum improvement in oxygenation, minimum ventilatory requirements, and lowest mortality rate were obtained by using 400 mg of surfactant per kilogram body weight. The surfactant used was a natural surfactant, as already used in neonates, and was given as a bolus. In this study the mortality of patients with ARDS could be decreased from 43.8% in controls to 17.6% in patients treated with exogenous surfactant therapy (79).

The second study by Amato et al. (80) was performed in 48 ARDS patients in two intensive care units. Twenty-five patients were ventilated with a lung protective strategy using a PEEP equal to or above the lower inflection point of the pressure volume curve of the lung (resulting in average PEEP levels of 14—18 cm H₂O), tidal volumes ≤ 6 ml/kg and peak inspiratory pressures ≤ 40 cm H₂O. The other patients were ventilated with tidal volumes of 12 ml/kg and normal PaCO₃ levels while PEEP was set to keep FiO₂ < 0.6 without hemodynamic impairment (average PEEP levels 8—11 cm H₂O). The survival analysis revealed a marked benefit of the lung protective strategy (80). The level of PEEP early in ARDS was the only factor positively correlated with improved survival in ARDS patients. The use of high plateau pressures and high difference between plateau pressures and PEEP (ΔP) was negatively correlated with a positive outcome (89).

This, there is a reduction in mortality by a more global "optimal ventilation strategy" in ARDS.

**FUTURE IMPLICATIONS FOR VENTILATORY TREATMENT OF PATIENTS WITH ARDS**

The transpulmonary pressure during spontaneous or mechanical ventilation in surfactant-deficient ARDS lungs creates high shear forces between open and closed alveoli due to interdependence of the alveoli causing
disruption of lung epithelial cells (20, 42). Research in animals indicates that this may lead to bacterial translocation and inflammatory mediator release. Rational ways to prevent the development of systemic inflammation and bacterial translocation in surfactant-deficient lungs and reduce mortality in ARDS patients are therefore directed at:

1) reducing shear forces and preventing further surfactant inactivation in lung parts that are still healthy by balancing the increase collapsive tendency of the alveoli by modes of ventilation which prevent end-expiratory collapse and which use minimal pressure swings (open lung concept) (43).

2) to reestablish a physiological surface tension at the air-liquid interface by application of exogenous surfactant during mechanical ventilation (exogenous surfactant therapy) (90).

If this concept is right, such treatments will prevent the release of inflammatory mediators from the lung and the transfer of bacteria and bacterial endotoxins to the bloodstream (Fig. 4). This will prevent the development of systemic inflammation with other organs being affected (Fig. 5) and may have an important influence on mortality rates of ARDS. The results reported by Gregory and Amato support this hypothesis (79, 80, 89).

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**Fig. 4.** Mechanical ventilation of a surfactant-deficient lung leads to the development of shear forces, inflammation mediator release, and bacterial translocation from the lung into the bloodstream, which may finally lead to the development of a generalized inflammation: multiple organ failure (MSOF). Important benefits in mortality from MSOF may therefore be achieved by lung therapies that are directed at reducing such shear forces (see text for details).
CONCLUSION

The main target of the treatment of acute respiratory failure is the prevention of ARDS by early treatment of its causes. In all cases in which the development of ARDS can not be prevented, surfactant replacement in combination with “non-traumatic” mechanical ventilation will be of greatest importance. The use of exogenous surfactant prevents end-expiratory alveolar collapse at low transpulmonary pressure. Moreover, during artificial ventilation all lung alveoli will have to be actively opened and have to be kept open at an FRC level which prevents surfactant depletion, while ventilating them with the lowest possible pressure differences. Deleterious shear forces on the lung epithelium will be prevented by these therapeutic measures. This will prevent the release of inflammatory mediators and the translocation of bacteria from the lung into the bloodstream through disrupted epithelium. Lung protective strategies may have an important role in preventing the transition from ARDS into MOF (Fig. 5) and mortality from MSOF.

Further research is necessary to investigate the prevention of mediator release and bacterial translocation by optimal ventilation strategies including partial liquid ventilation (91) and exogenous surfactant therapy in the early stages of lung injury and by ventilator strategies such as pressure-controlled inversed ratio ventilation or high frequency ventilation.
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